tion with the comment that "Hirayama was unable to assess the accuracy of the diagnoses listed on the death certificate[s]."

Assessing the Hirayama data from the following array

Lung Cancer Present	ETS Exposed	
	Yes	No
Yes	163	37
No	69 482	21 858

EPA (USEPA 1992) reported a crude relative risk of 1.38 (90% C.I. 1.03-1.87). There is potential disease misclassification, however, for all 200 lung cancer cases, with more than four and one-half times as many cases among those exposed to ETS than among those not exposed.

If as few as four of the 163 lung cancer cases exposed to ETS were disease misclassified—i.e., were not primary lung carcinomas—the relative risk would be a statistically nonsignificant 1.34 (C.I. 0.99-1.71).

Of the 31 epidemiological studies in the data base of the EPA Review Draft, all lung cancer cases of 12 studies were reported to have been histologically or cytologically confirmed. In 14 studies, from 2% to 100% of the lung cancer cases had not been definitively confirmed, while in 5 studies, the method and extent of verification were not reported.

Among the 27 case-control studies, ten had 10% or more of lung cancer cases not definitively confirmed as primary carcinomas, including 45 (83%) of 54 cases in the Liu study, 40 (43%) of 94 cases in Akiba, 14 (35%) of 40 cases in Trichopoulos, 108 (26%) of 417 cases in Wu-Williams, and 46 (19%) of 246 cases in Gao, for a total of 253 (30%) of 851 "lung cancer cases" not confirmed as primary. For all case-control studies where the extent of diagnosis confirmation was established, EPA data show 302 lung cancer cases were not definitively confirmed.

Of the cohort or prospective studies, none of the 200 lung cancer cases in the Hirayama study were known to have been confirmed as primary, and the Review Draft notes the absence of information on the other three cohort studies. It also notes that in 10 studies "secondary lung cancers" had not been excluded.

The EPA Review Draft shows 64% of the cases were classified as exposed to ETS, so that there may be nearly twice the likelihood of disease misclassification among "cases" classified as exposed to ETS as among those not exposed. However, any assumptions about the distribution of disease misclassifications in specific studies or in the overall data base would be entirely speculative and insupportable.

The failure to give appropriate consideration in the EPA Review Draft to the significant potential for disease misclassification reduces confidence in risk estimates derived from the data and raises serious questions about public health policies based on such studies.

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This review was conducted at the request of The Tobacco Institute; the statements expressed herein are solely those of the author.

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LETTER TO THE EDITOR

IMPLICATIONS FOR DISEASE MISCLASSIFICATION IN EPIDEMIOLOGICAL STUDIES OF LUNG CANCER RISK FOR NONSMOKERS EXPOSED TO ENVIRONMENTAL TOBACCO SMOKE

Dear Editor:

The U. S. Environmental Protection Agency (EPA) appears to have diminished or dismissed the potentially significant role of disease misclassification in its review of lung cancer risk in nonsmokers reportedly exposed to environmental tobacco smoke (ETS). After reviewing 31 epidemiological studies of lung cancer risk in nonsmokers married to smokers v. those married to nonsmokers (USEPA 1992), EPA concluded that the statistics support the conclusion of a significant risk for nonsmokers exposed to ETS. Adjustments were made for potential misclassification of smoker status, but EPA made no attempt to adjust for potential disease misclassification, which is more likely to result in overestimation than underestimation of relative risk.

Disease misclassification arises when "lung cancer cases" are not primary lung carcinomas but are secondary cancers that have metastasized to the lung from primary tumors originating in other body tissues. Definitive diagnosis of primary lung cancer requires histological or cytological examination of lung tissue.

Diagnoses based on other than histological or cytological examination are equivocal, at best. American Cancer Society researchers noted (Garfinkel et al. 1985) one U.S. study in which 13% of hospital cases were found to be improperly identified as primary lung cancers.

The EPA Review Draft acknowledges the possibility of disease misclassification in epidemiological studies, commenting that it creates "bias toward the null" without further explanation or acknowledgement that such bias is not consistent in the direction of bias nor in magnitude from study to study.

Relative risk in epidemiological studies is determined from the data arrayed as follows:

Lung Cancer Present	ETS Exposed	
	Yes	No
Yes	a	b
No	c	d

with the odds ratio for case-control studies calculated from the formula, OR = ad/bc, and the relative risk for cohort or prospective studies from the formula, RR = (a/a+c)/(b/b+d). (For editorial simplicity, the term relative risk is often used for both kinds of studies and determinations.)

The potential effect of disease misclassification can be illustrated in the study of Hirayama (1984) in Japan, which was among the earliest of the epidemiological assessments said to find lung cancer risk in nonsmokers married to smokers. Hirayama (1984), along with the early Greek study (Trichopoulos et al. 1981) were the only studies in the data bases of the National Research Council (NRC 1986) and the Surgeon General's (USSG 1986) reports to claim statistically significant increased risk for nonsmokers married to smokers.

The Hirayama study was based on 91 540 death certificates, of which 200 reportedly were for nonsmokers who had died of lung cancer. Twenty-one (10.5%)of the certificates reported cause of death determined by autopsy, but the type of lung cancer was not specified, and there is no basis for believing that many were histologically or cytologically confirmed as primary lung carcinomas. For the remaining 179 (89.5%) cases, no basis for the classification of death was reported, indicating that at least 89% and up to 100% of the lung cancer cases in Hirayama's study are of questionable disease classification. The Surgeon General's Report (USSG 1986) noted the potential for disease misclassifica-

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